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Infection and inflammation in cystic fibrosis: A short review

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Abstract

In most patients with cystic fibrosis (CF) life expectancy is limited due to a progressive loss of functional lung tissue. Already very early in life a persistent neutrophylic inflammation can be demonstrated in the airways. The cause of this inflammation, the role of CFTR and different CF specific bacteria like *Pseudomonas aeruginosa* are not well understood. This short review summarises the current understanding and hypothesis of the origin of this complicated process of inflammation and infection. Better understanding of this process may lead to the development of new treatment modalities of CF lung disease and consequent improvement of life expectancy.
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Keywords: Cystic fibrosis; Inflammation; Infection; CFTR; *Pseudomonas aeruginosa*

1. Introduction

Cystic Fibrosis (CF) is an autosomal recessive disorder with a potential lethal outcome among white populations, affecting approximately 1:3300 live white births [1]. CF is caused by mutations in a single gene on chromosome 7 that encodes the cystic fibrosis transmembrane conductance regulator (CFTR) [2]. These mutations cause disruption of CFTR function within epithelial cells [3]. Although many organs are affected in CF, lung disease is the major cause of morbidity and virtually all mortality. The lungs, including mucus glands, are structurally normal at birth [4]. Soon after birth excessive endobronchial inflammation in the small airways has been demonstrated in both sputum culture positive and sputum culture negative patients. Broncho-alveolar lavage (BAL) fluid shows a predominantly neutrophil inflammation with elevated interleukin(IL)-8 and neutrophil elastase [5–8]. This persistent inflammation is the major cause of progressive lung injury and destruction leading to a decrease in lung function. This progressive loss of lung function is the main reason for the limited life expectancy of most patients with CF. Understanding the pathophysiology of lung inflammation and thereby the pathogenesis of lung disease in CF is needed to improve current and develop future treatment modalities.

2. Defective CFTR and initiation of lung infection and inflammation

Because inflammation has been demonstrated in culture negative patients it has been postulated that, apart from infection, defective CFTR itself may play an important role in the excessive inflammation in the airways. As foetal CF lungs are not grossly impaired as demonstrated by histopathological studies, CFTR appears not to cause inflammation in the lungs before birth. This is in sharp contrast with other organs like the vas deferens, intestine and pancreas that can be severely impaired during gestation. Therefore it is doubtful that CFTR alone is responsible for the initiation of lung inflammation with consequent tissue destruction. Most likely, the observation that excessive inflammation is present in patients with negative cultures may be due to the regional variability of inflammation and infection in different parts of the lung [8]. Another explanation may be that bacteria below detectable levels are responsible for lung inflammation.

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Although it is doubtful that defective CFTR itself initiates inflammation, it may enhance or contribute to the inflammatory response to infection. Two hypothesis have been proposed that may contribute to the initiation of infection and inflammation in CF.

2.1. The salt depletion hypothesis

In this hypothesis the airways may be compared to sweat glands. The epithelial cells of the airways regulate the salt concentration in the airway surface liquid (ASL). Due to defective CFTR salt concentrations in the ASL are elevated. The function of innate antimicrobial peptide defensins is critically dependent on the ASL salt concentration.

In vitro it has been shown that defensins are inactivated by salt concentrations higher than 50 mmol/L thereby facilitating infection and bacterial growth [9].

2.2. The isotonic low volume hypothesis

In this hypothesis water permeable airway epithelia regulate the volume of the ASL.

Abnormal sodium absorption together with defective CFTR with consequent failure to secrete chloride leads to water and volume depletion of the ASL in an isotonic environment. Volume and water depletion occurs in the ASL and the periciliary fluid leading to increased viscosity in both compartments and consequent impaired mucociliary clearance. Bacteria are trapped in the tenacious mucus layer and consequently lead to chronic infection [10,11].

3. CFTR and Pseudomonas aeruginosa

Initiation of (chronic) infection can probably be explained by the qualitative changes in the ASL as has been described above. This does however not explain why patients with CF are infected with specific micro-organisms, especially *P. aeruginosa*.

There are a number of hypothesis that try to explain the unfavourable relationship between CF and *P. aeruginosa*.

3.1. CFTR may act as a specific receptor for P. aeruginosa

CFTR, apart from its function as a chloride ion channel, appears to act as a receptor for epithelial cell internalisation of *P. aeruginosa* on the airway surface [12–14]. Therefore, mutant CFTR results in reduced binding of *P. aeruginosa* and consequent reduction of *P. aeruginosa* clearance from the airways of patients with CF.

3.2. CFTR may influence bacterial adherence to epithelial cells

Epithelial cells of CF airways demonstrate a greater adherence to piliated strains of *P. aeruginosa* [15–17]. Expression of wild type CFTR in CF cell lines reduces the adherence of *P. aeruginosa*. Additionally, adherence of *P. aeruginosa* is greater in cell lines from patients homozygous for ΔF508 compared with heterozygotes and carriers [18]. The underlying process of this phenomomenon is not well understood although an increase in asialoganglioside-1 receptors in CF epithelial cells may play a significant role.

4. Bacteria and lung inflammation

Virtually all patients with CF are chronically infected with one ore more bacterial species.

The inflammatory response to infection appears to be more intense in patients with CF compared to non-CF patients. Additionally, it has been shown that the number of colony forming units in BAL fluid is directly related to the intensity of the inflammatory response with a significant increase in the number of inflammatory cells and an increase in IL-8 concentrations [19].

Early infection of the CF airways is mostly caused by *Staphylococcus aureus* and *Haemophilus influenza* [20]. Of more significance is chronic infection with *P. aeruginosa*. When initial colonization/infection with non-mucoid strains is not sufficiently treated, most patients become chronically infected with mucoid strains of *P. aeruginosa*. The prevalence of chronic infection with *P. aeruginosa* increases with age and is accompanied by a decrease in the prevalence of both *H. influenza* and *S. aureus* [20]. Chronic infection is prevalent in about 80% of all patients with CF. Recent studies, especially following patients diagnosed by neonatal screening, have shown that infection with *P. aeruginosa* occurs already at very young age [21]. Positive antibody response to *P. aeruginosa* was found in children with a mean age of 15 months, about 12 months before first cultures were positive. Also in young, non-sputum producing children it was found that throat swabs frequently showed positive cultures for *P. aeruginosa* [22].

In chronic infection with alginate-coated mucoid strains of *P. aeruginosa*, eradication is nearly impossible. Even with intensive antibiotic regimens, mucoid *P. aeruginosa* cannot be eradicated, probably because of poor penetration of antibiotics into anaerobic sputum plugs and rapid development of mutator strains, which show enhanced resistance to antimicrobial drugs [23,24].

Acquisition and consequent chronic infection with mucoid strains of *P. aeruginosa* leads to an increase in the endobronchial inflammatory response to infection. It has been shown that CF cell lines produce more pro-inflammatory cytokines than normal cell lines in response to *P. aeruginosa* [25]. This “overproduction” of pro-inflammatory cytokines can be found in the ELF of CF airways [26]. Also significantly lower levels of the anti-inflammatory cytokine IL-10 , which inhibits the production of pro-inflammatory cytokines, are found. This imbalance of anti-

inflammatory and pro-inflammatory cytokines results in an excessive and persistent inflammation in the CF airways. As a result lung function deteriorates more rapidly in *P. aeruginosa* positive patients compared with CF patients negative for *P. aeruginosa* [27,28].

5. Conclusion

After being born with anatomically "normal" lungs, patients with CF develop endobronchial inflammation at very young age. This endobronchial inflammation is the result of an overreaction of the immunological response to infection which occurs due to CFTR related abnormalities in the ASL. The unfavourable relation of CF airways with *P. aeruginosa* results in chronic infection in the majority of patients, often already at a very young age. Chronic infection with *P. aeruginosa* further enhances the endobronchial inflammatory response with an imbalance between pro- and contra inflammatory mediators leading to destruction of lung tissue and a decrease in pulmonary function.

Better understanding of this process may offer new treatment modalities directed at the prevention of chronic infection with *P. aeruginosa* and an inhibition of the inflammatory response.

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